The Trial of Intensified Medical Therapy in Elderly patients with Congestive Heart Failure (TIME-CHF)

Chapter XII

Valorisation

The present work is a summary of pre-specified analyses and post-hoc studies of the largest study on natriuretic peptide-guided therapy in oldest and most comorbid heart failure population. None of the studies has provided definite results on a particular topic but we think that some results have extended existing concepts and others form the basis for pathophysiological considerations and future studies. Thus, we think that the present work represents a valuable contribution to the literature.

The findings on worsening renal function (WRF) are important as they provide reassurance that the recently developed concept of "pseudo-WRF" is relevant not only for the acute heart failure setting but also the chronic setting. The results have direct implications for clinical practice in that doctors do not have to worry too much about changes in serum creatinine in heart failure patients as long as patients do clinically well during the up-titration of neurohormonal blockade, and that reduction of heart failure therapy is not required in this setting. On the other hand the findings underscore the notion that a therapy mainly consisting of high loop diuretic doses represents a marker and maybe also a mediator of a poor prognosis, and maximal efforts are required to maximize neurohormonal blockade and minimize loop diuretic doses. The data also highlight the importance of close monitoring of serum creatinine and potassium, in particular in elderly and comorbid patients.

The findings on heart rate are novel in that they clearly show that the prognostic impact of heart rate depends on age, a finding which did not well emerge from the SHIFT data because this study did not include many older patients. This has clinical implications with regards to the practice of the up-titration of betablockers and the use of ivabradine in elderly patients. Both classes of drugs are recommended in guidelines based on studies in relatively young patients, but the optimal heart rate in sinus rhythm in elderly patients will have to be defined in future studies. In addition, we have shown that we will have to think about the heart rate target in patients with heart failure and atrial fibrillation and the best way we should achieve this. This is largely unknown, and our and other studies have indicated a need for further research in this area. Although a simple parameter, our findings on delta heart rate are novel and promising. It would be very attractive if a simple bedside test could help to refine the prognostic assessment in a significant manner. However, further studies with delta heart rate measured in a more standardized fashion and exploring its pathophysiological correlates as well as the confirmation of the prognostic data in other cohorts are required.

The concept of natriuretic peptide-guided heart failure therapy has been evaluated in several studies, and findings are consistent in that younger patients with HFrEF derive benefit. We were the first to shown that the intervention of natriuretic peptide-guided therapy has a sustained prognostic impact even after termination of NT-proBNP-guided up-titration of therapy. Second, we have shown that the concept of natriuretic peptide-guided therapy seems not to work in patients with HFpEF in whom left ventricular structure and function clearly differs from that in HFrEF. Thus, TIME-CHF including the present analyses has provided an important contribution to define the application of natri-

uretic peptide-guided therapy in heart failure. On the other hand, TIME-CHF has revealed that future research must address the question how to tailor heart failure therapy in elderly patients in general, and particular in those with HFpEF for whom there is still no drug with established prognostic benefit.